REMARKS

Claims 71, 97, and 103-110 are pending after entry of this paper. Claims 71, 82-92, 97, 104, 106, 108, and 110 have been rejected. Claims 105, 107 and 109 have been withdrawn from consideration. Claims 1-70, 72-81, and 93-96 have been previously cancelled without prejudice. Claims 82-92 and 98-103 have been currently cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a divisional or continuing application.

Claim 71 has been amended to replace the "method for treatment of reversible abnormal changes in pH of nucleated and non-nucleated cells" with the "method for normalizing an acid-base balance of nucleated and non-nucleated cells." This amendment does not change the scope of the claim. Support for this amendment can be found throughout the instant specification and claims as filed.

Claims 103-110 have been amended to place the claims into the proper dependence.

No new matter has been introduced by the claim amendments presented herein. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Rejections under 35 U.S.C. § 112, first paragraph

Claims 82, 84, 85, 87, 89, 91, 92, 98, 100, and 102 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims allegedly recite specific diseases that are not described in the specification. (Office Action; pgs. 4-7). Applicants respectfully traverse this rejection.

However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have cancelled claims 82, 84, 85, 87, 89, 91, 92, 98, 100, and 102. Thus, this rejection is now moot. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejections to claims 82, 84, 85, 87, 89, 91, 92, 98, 100, and 102.

Response to Rejections under 35 U.S.C. § 103(a)

Claims 71, 82, 85, 86, 90, 93-96, 99, 103, 104, 106, 108, and 110 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Henry, et al. (U.S. Patent 6,953,799, already of record). According to the Office Action, Henry discloses a compound such as luminol that can be allegedly administered to a patient to treat "hosts with diseases involving impaired or aberrant intracellular redox states, which affects the membrane proton gradient, resulting in intracellular acidosis, and causes oxygen deficiency in cells and excessive formation of the free radical superoxide" (Office Action; p. 8). In response to applicants' previous arguments dated October 27, 2010, the Office Action acknowledges that Henry is silent about treating patients with the acid-base imbalance as recited in claim 71, however, the Office Action contents that Henry teaches treating diseases with impaired or aberrant intracellular redox states, which affect the membrane proton gradient, therefore "would obviously result [in] an abnormal change in pH." *Id.* Applicants respectfully traverse this rejection based on the following reasons.

Applicants do not dispute that Henry discloses the use of the phthalazine diones to primarily support metabolically stressed cells in a host by buffering intracellular thiol redox status of the aerobic metabolism in the stressed mitochondria. (Henry, col 2, lines 35-40, col 4, lines 33-36, col. 4, line 65 – col. 5, line 8). Henry also discloses that phthalazine diones target

electron flow in mitochondria, and thus control ATP production. However, it is well accepted in the art that acidosis is caused by cytosolic (nonmitochondrial) catabolism. There is no evidence to the contrary. Yet, the Office Action draws a conclusion that "[a]ffecting the membrane proton gradient would obviously result [in] an abnormal change in pH based [on] what one of ordinary skill in the art would have understood regarding the role of the concentration of H^+, or pH, in defining the membrane proton gradient." *Id.* Applicants respectfully assert that such conclusion cannot be drawn from the teachings of Henry and is not supported in the art as applicants previously demonstrated in the response submitted on October 27, 2010.

Thus, applicants respectfully maintain that the malfunction of the proton gradient in the mitochondria "would [not] obviously result [in] an abnormal change in pH" suggested in the Office Action as a common knowledge in the art. (Office Action; pg. 10). "[W]hen the PTO seeks to rely upon a chemical theory, in establishing a *prima facie* case of obviousness, it must provide evidentiary support for the existence and meaning of that theory." *In re Grose*, 592 F.2d 1161, 1167-68 (CCPA 1979) (see MPEP 2144.03). While applicants provided plethora of evidence contrary to this position taken by the Patent Office, the Office Action still does not set any "rational underpinning" to support the legal conclusion of obviousness as to why the buffering of the thiol redox status of the aerobic metabolism in the stressed mitochondria would create acid-base imbalance due to failure of withdrawing excessive quantity of protons from the cell. See *KSR*, 127 S. Ct. at 1741 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Broad conclusory statements of suggestion or motivation standing alone are not sufficient. *Id.*

Thus, applicants respectfully assert that Henry does not make obvious the claimed method because the mechanism of action of treatment has a direct bearing on which patient population is selected. While Henry teaches a method of regulating thiol or oxygen redox states,

the patients would be selected that show redox imbalance of the aerobic metabolism in the mitochondria (col 4, line 65 – col. 5, line 2), whereas the instant method is directed to treating acid-base imbalance in nucleated and non-nucleated cells, by administering to a subject in need of such treatment a pharmaceutically-effective amount of a biologically-active compound in order to normalize the endocellular pH to the physiologically acceptable levels. Thus, at least on this ground, applicants respectfully assert that claims 71, 97, 103, 104, 106, 108, and 110 are not rendered obvious by the suggested combination of cited reference and the common knowledge in the art. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) as being obvious over Henry.

Response to Rejections under 35 U.S.C. § 103(a)

Claims 71, 82, 86, 88, 90, 97, 98, 101-104, 106, 108, and 110 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Minin, et al. (U.S. Patent 5,512,573, already of record) in view of Henry. According to the Office Action, Minin discloses the administration of luminol as an antioxidant. (Office Action; pgs. 12-13). In response to applicants' previous arguments dated October 27, 2010, the Office Action acknowledges that Minin is silent about treating patients with the acid-base imbalance as recited in claim 71. However, the Office Action contents that it would be obvious to combine Minin with Henry that teaches treating diseases with impaired or aberrant intracellular redox states, which affect the membrane proton gradient, therefore "[o]ne of ordinary skill in the art would have been motivated to combine Minin et al. in view of Henry eta al." Id. Applicants respectfully traverse this rejection based on the following reasons.

The knowledge imparted from Minin and Henry would still be insufficient to arrive at the claimed invention. The Patent Office may not evaluate the invention "part by part," using the invention as a "roadmap to find its prior art components." *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.* 411 F.3d 1332, 1337 (Fed. Cir. 2005). Hindsight reconstruction is impermissible. *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998). While Minin discloses a method to use luminol as an antioxidant and Henry discloses a method of buffering intracellular thiol redox status of the aerobic metabolism in the stressed mitochondria, the Office Action does not set any "rational underpinning" to support the legal conclusion of obviousness as to why those skilled in the art would treat an acid-base imbalance based on such disclosures. See *KSR*, 127 S. Ct. at 1741 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Broad conclusory statements of suggestion or motivation standing alone are not sufficient. *Id.* In other words, even if, for an argument sake, those skilled in the art could combine the teachings of Minin and Henry because both disclose luminol, it is not readily apparent why would they treat the acid-base imbalance in light of applicants argument that the mitochondrial proton gradient malfunction does not support the conclusion of the acid-base imbalance since it is well accepted in the art that acidosis is caused by cytosolic (nonmitochondrial) catabolism.

Applicants have not simply arranged "old elements with each performing the same function it had been known perform." *KSR*, 127 S. Ct. at 1740. To the contrary, applicants have created a novel and unobvious method of treating acid-base imbalance. Thus, applicants have created a method that, when considered as a whole, provides a benefit that exceeds the mere sum of its parts. Thus, at least on this ground, applicants respectfully assert that claims 71, 97, 103, 104, 106, 108, and 110 are not rendered obvious by the suggested combination of cited

references. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejections to claims 71, 97, 103, 104, 106, 108, and 110.

CONCLUSION

For at least the reasons stated above, Applicants respectfully request entry of this response and allowance of the claims. However, in the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

DEPOSIT ACCOUNT AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-4827, Order No. 1004398-001US.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No 50-4827, Order No. 1004398-001US.

Respectfully submitted,

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Dated: June 30, 2011

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